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Bowel movement alterations predict the severity of diverticular disease and the risk of acute diverticulitis: a prospective, international study

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Background/Aims: Patients with diverticular disease (DD) frequently have abnormal bowel movements. However, it is unknown whether the entity of these alterations is associated with the severity of DD. We aimed to assess bowel habits and their relationship with the severity of DD according to Diverticular Inflammation and Complication Assessment (DICA) classification, Combined Overview on Diverticular Assessment (CODA) score, and fecal calprotectin (FC). **Methods:** An international, multicenter, prospective cohort study was conducted in 43 centers. A 10-point visual analog scale (VAS) was used to assess the severity of constipation and diarrhea. The association of constipation and diarrhea with DICA classification, CODA score, and basal FC was tested using non-parametric tests. Survival methods for censored observations were applied to test the association of constipation and diarrhea with the incidence of acute diverticulitis over a 3-year follow-up. **Results:** Of 871 patients with DD were included in the study. Of these, 208 (23.9%) and 199 (22.9%) reported a VAS score for constipation and diarrhea at least 3 at baseline, respectively. Higher constipation and diarrhea scores were associated with increasing DICA classification, CODA score and basal FC ($P<0.001$). Constipation and diarrhea scores were independently associated with an increased hazard of developing acute diverticulitis (hazard ratio $[HR]_{constipation}=1.15$ per 1-VAS point increase, 95% confidence interval [CI], 1.04–1.27; $P=0.004$; and $HR_{diarrhea}=1.14$; 95% CI, 1.03–1.26; $P=0.014$, respectively). **Conclusions:** In newly diagnosed patients with DD, higher endoscopic and combined scores of DD severity were associated with higher scores of constipation and diarrhea at baseline. Both constipation and diarrhea were independent prognostic factors of acute diverticulitis. **(Intest Res, Published online)**

Key Words: Bowel frequency; Diverticular diseases; Diverticular Inflammation and Complication Assessment classification; Fecal calprotectin; Acute diverticulitis

INTRODUCTION

The prevalence of diverticulosis of the colon and its clinical manifestation, diverticular disease (DD), have shown significant increments in the last few years.[1] The severity of DD is currently scored according to clinical,[2] radiological,[3] and endoscopic classifications,[4] and much is known about its management.[1] Despite this, little is currently known about the pathogenesis of diverticulosis and DD,[5] in particular about the role of fecal output and its severity in the pathophysiology of the disease.

Constipation has been considered the mainstay of the disease for many years,[5] but recent studies seem to exclude this association.[6,7] At the same time, diarrhea seems to be more frequent in patients with diverticulosis,[8,9] and patients reporting diarrhea seem to be at higher risk of acute diverticulitis.[10] However, this association has yet to be investigated in depth in patients with DD, and no data are currently available about the relationship between the type and entity of fecal output and the severity of DD.

DICA (Diverticular Inflammation and Complication Assessment) endoscopic classification (Supplementary Table 1) and CODA (Combined Overview on Diverticular Assessment) clinical score (Supplementary Table 2) have recently shown their effectiveness in predicting the outcome of the DD.[4] Their predictive role was enhanced when associated with fecal calprotectin (FC) expression.[11]

This study aimed to assess the fecal output of patients with diverticulosis and DD and investigate the association of bowel habits with the severity of the DD, measured according to the DICA endoscopic score, CODA clinical score, and FC expression.

METHODS

1. Study Design and Study Aims

This is a *post-hoc* analysis of a previously published, multicenter, prospective cohort study including patients with diverticulosis/DD diagnosed by endoscopy in 43 international centers in Italy, Germany, United Kingdom, Poland, Romania, Lithuania, Brazil, and Venezuela.[4] In detail, the studied population is a subgroup of 871 patients from the original cohort of 2,198 patients used to validate the DICA endoscopic classification for diverticulosis/DD and to develop the CODA clinical score for diverticulosis/DD,[4] in which all patients underwent FC dosing at the baseline visit.

2. Participants

In the original prospective study, only patients at the first diagnosis of diverticulosis/DD (i.e., newly diagnosed DD patients) were enrolled. A common database to collect demographic and clinical data was built. Regarding symptoms, simplified definitions of constipation: the passage of fewer than 3 stools per week and/or having a difficult time in passing stools and

diarrhea; the passage of more than 3 stools per day and/or often semiliquid or liquid stools consistency, were adopted.[12] They were based on the Bristol Stool Form Scale.[13]

Inclusion criteria were age >18 years, and first endoscopic diagnosis of diverticulosis; exclusion criteria were radiological signs (by abdominal computed tomography or by ultrasounds) of acute diverticulitis (defined as inflammation of colonic wall harboring diverticula with fat stranding, and with or without complications such as abscesses, stenosis or fistulas, namely uncomplicated or complicated diverticulitis)[1]; inflammatory bowel diseases; ischemic colitis; infectious colitis; prior colonic resection; patients with severe liver failure (Child-Pugh C); patients with severe kidney failure; pregnant women; women of childbearing potential not using a highly effective method of contraception; patients with current use or who have received any laxative agents <2 weeks prior to the enrollment; patients with recent use or who have received mesalamine compounds <2 weeks prior to the enrollment; patients with current use or who have received any probiotic agents 2 weeks prior to the enrollment; nonsteroidal anti-inflammatory drug use (except for acetylsalicylic acid ≤100 mg/day) <1 week prior to the enrollment; patients who have received treatment with antibiotics (even those not absorbed) <2 weeks prior to the enrollment; inability to comply with study protocol and to give informed consent to the procedure; patients with or history of cancer, of any origin, within 5 years before enrollment; history of alcohol, drug, or chemical abuse; any severe pathological condition interfering with the proper study execution. Further data about the study's design were reported in the original study.[4]

Patients were scored according to DICA classification and CODA score.[4] Since our initial study protocol did not plan centralized laboratory analysis of FC, we considered only valid FC measurements deriving from quantitative assays expressed in μg/g to homogenize and increase the comparability across centers.

Our aims were: (1) to evaluate the frequency of constipation and diarrhea in patients with diverticulosis/DD; (2) to evaluate the severity of constipation and diarrhea in those patients; (3) to estimate the association between constipation and diarrhea with the severity of diverticulosis/DD according to DICA classification, CODA score and FC expression at baseline[14]; and (4) to assess the association between constipation and diarrhea and development of acute diverticulitis over the follow-up.

3. Statistical Analysis

Descriptive statistics include medians and interquartile ranges (IQRs) for continuous variables and frequency analyses (percentages) for categorical variables. The frequency and severity of constipation and diarrhea were measured using a 10-point visual analog scale (VAS), ranging from 0: absence to 10: maximal severity. The association of constipation and diarrhea with the severity of diverticulosis/DD was assessed by comparing the 10-point VAS scores across groups defined by the DICA classification, CODA score and basal FC. The 2-sample Wilcoxon rank-sum and the Kruskal-Wallis tests were used to compare continuous variables across groups.

The association of constipation and diarrhea, measured at baseline, with the risk of developing acute diverticulitis was assessed by time-to-event (survival) methods for censored observations. Time-to-event was defined as the time (in months) from the baseline visit until the event date or censoring. Cox regression was performed by running 2 univariable models testing the effects of constipation and diarrhea separately as continuous variables. We also examined whether the associations of constipation and diarrhea with acute diverticulitis were independent by fitting a multivariable model including both constipation and diarrhea jointly while adjusting for the potential confounding effect of age and sex.[9,10] A previous study on the association between bowel movements and diverticulitis found that age categories, body mass index, physical activity, laxative use or fiber intake did not modify the association.[10] As the current study has an etiological scope, we considered this evidence and adjusted only for sex and age as a continuous variable. We retained the adjustment by age as the previous study considered age as a categorical variable, which could have yielded a lack of statistical power to detect an effect. The Kaplan-Meier estimates were employed to plot the cumulative incidence of diverticulitis in groups of patients defined by the absence (VAS=0) or presence (VAS>0) of any symptoms of constipation and diarrhea. Log-rank tests were performed to compare the plotted curves. Two-tailed $P<0.05$ was considered to indicate statistical significance. Stata software version 17 (StataCorp LLC, College Station, TX, USA) was used for analysis.

4. Ethics Approval

The study was conducted according to the 1975 World Medical Association Declaration of Helsinki and was approved by the Ethic Committees of the coordinator center (Prot.64/SCE/2015) and all participating centers. All study participants

provided informed written consent before the endoscopic investigation and to participate in this study.

RESULTS

Baseline demographic and clinical characteristics are reported in Table 1. Patients were predominantly males (50.4%) with a median age of 65 years (IQR, 56–72 years). They were slightly overweight (median body mass index, 26 kg/m^2; IQR, 23.2–28.9 kg/m^2), and 28.2% were smokers. Most patients (56.0%) had a DD corresponding to the DICA 1 classification, 32.1% DICA 2, and 11.9% DICA 3. After considering DICA classification, age and abdominal pain score, the CODA score was computed for each patient (median CODA score, 10; IQR, 7–16). Basal FC varied widely across patients, ranging from 8 to 1,800 μg/g, with a median of 25 μg/g (IQR, 12–70 μg/g).

Sixty-five acute diverticulitis events occurred during an average follow-up of 2.8 years. The cumulative incidence of diverticulitis was 26.5 per 1,000 person-years, corresponding to an estimated 3-year risk of 7.6% (95% confidence interval [CI], 6.0%–9.6%).

The scores of constipation and diarrhea increased with increasing DICA classification (Kruskal-Wallis test, $P<0.001$) (Fig. 1A and B) and increasing CODA scores (Kruskal-Wallis test, $P<0.001$) (Fig. 1C and D). Similarly, higher scores of constipation and diarrhea were associated with higher basal FC (Wilcoxon rank-sum test, $P<0.01$) (Fig. 1E and F).

Cox regression analyses evaluated the effect of constipation and diarrhea on the incidence of acute diverticulitis. At the univariable analysis, we found evidence of a significant association between the scores of constipation and diarrhea and the risk of developing acute diverticulitis over the 3-year follow-up (hazard ratio $[HR]_{constipation}$, 1.12 per 1-VAS point increase; 95% CI, 1.02–1.23; $P=0.019$; $HR_{diarrhea}$, 1.11 per 1-VAS point increase; 95% CI, 1.00–1.22; $P=0.047$, respectively).

The results were confirmed in the multivariable model, which tested the association of both variables jointly and adjusted them by age and sex. There was a 15% increase in the hazard of acute diverticulitis per each point increase in the score of constipation ($HR_{constipation}$, 1.15; 95% CI, 1.04–1.27; $P=0.004$) and a 14% increase in the hazard of acute diverticulitis per each point increase in the score of diarrhea ($HR_{diarrhea}$, 1.14; 95% CI, 1.03–1.26; $P=0.014$) (Table 2). Both effects were independent of each other.

The estimated 3-year cumulative probability of diverticulitis was 5.9% (95% CI, 4.1%–8.3%) in patients without symptoms

Table 1. Baseline Demographic and Clinical Characteristics of the Study Population

Characteristic	Value (n = 871)
Age (yr)	65 (56–72)
≥ 65	451 (51.8)
Male sex	439 (50.4)
Body mass index (kg/m^2)	26.0 (23.2–28.9)
≥ 30	166 (19.1)
Smoking	
Smokers	246 (28.2)
Non-smokers	513 (58.9)
Ex-smokers	112 (12.8)
Appendectomy	224 (25.7)
Presence of co-morbidities	
Charlson's score	3 (2–4)
Charlson's score > 3	220 (25.2)
Presence of any symptom	682 (78.3)
Cumulative symptom score[a]	8 (2–13)
> 7	441 (50.6)
Abdominal pain	2 (0–5)
> 2	404 (46.4)
Bloating	2 (0–4)
> 2	371 (42.6)
Constipation	
Absent (0)	539 (62.0)
Mild (1 or 2)	123 (14.1)
Moderate to severe (> 2)	208 (23.9)
Diarrhea	
Absent (0)	561 (64.4)
Mild (1 or 2)	111 (12.7)
Moderate to severe (> 2)	199 (22.9)
DICA classification	
1	488 (56.0)
2	279 (32.1)
3	104 (11.9)
CODA score	10 (7–16)
Fecal calprotectin (μg/g)	25 (12–70)
> 90	151 (17.3)

Values are presented as median (interquartile range) or number (%).
[a]The cumulative symptom score ranges from 0 to 40 points. It is obtained by adding the points regarding abdominal pain, meteorism, constipation, and diarrhea as measured on a 10-point visual analog scale.
DICA, Diverticular Inflammation and Complication Assessment; CODA, Combined Overview on Diverticular Assessment.

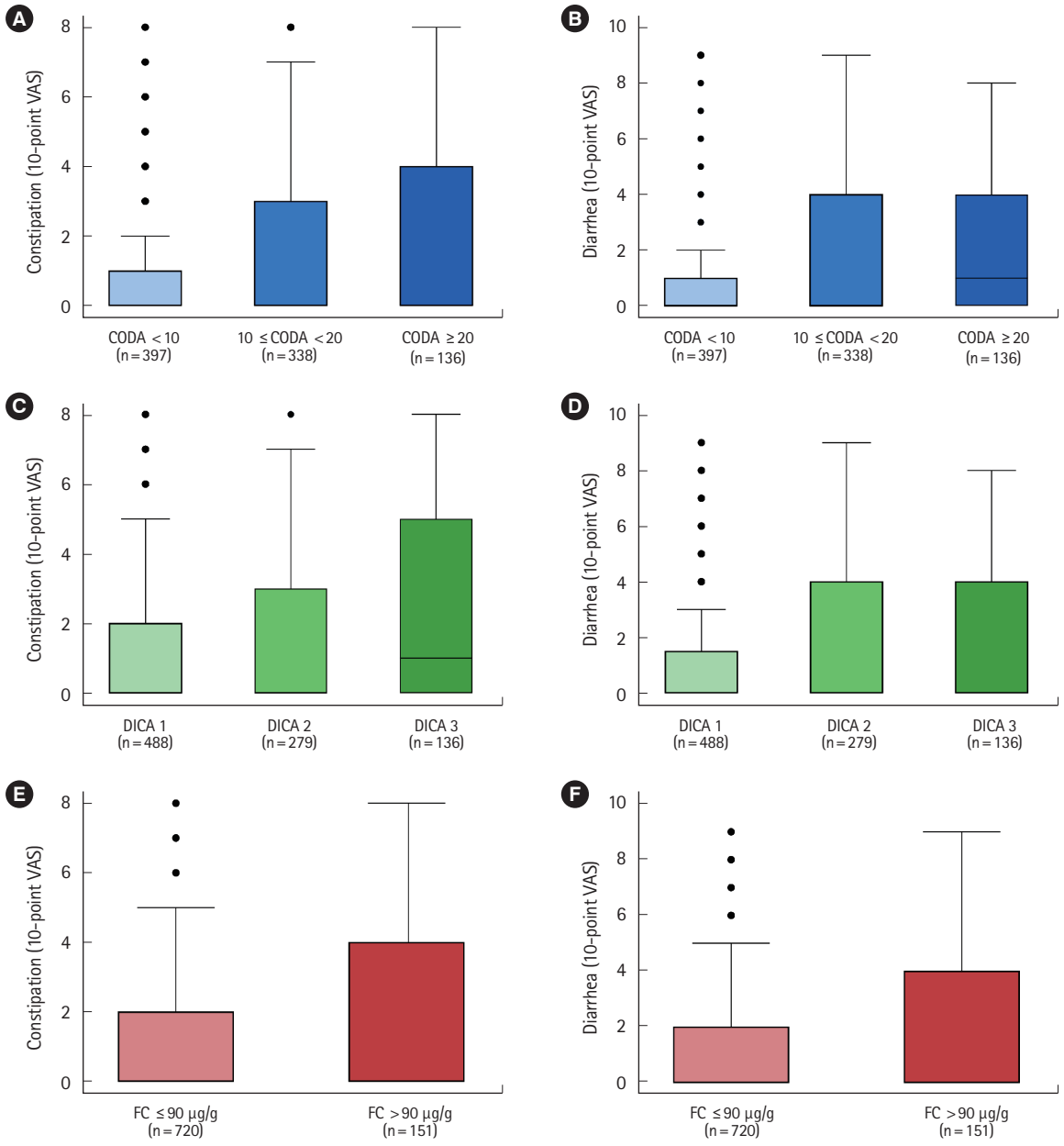

Fig. 1. Box plots showing the distribution of symptoms scores for constipation and diarrhea (10-point VAS) across groups of patients defined by DICA endoscopic classification levels (A, B), CODA score (C, D), and basal FC (E, F). Constipation and diarrhea 10-point VASs were tested as continuous variables across the DICA classification levels and CODA scores by applying the Kruskal-Wallis test (A-D; $P<0.001$) and across the 2 categories of FC by using the Wilcoxon rank-sum test (E, F; $P<0.01$). VAS, visual analog scale; DICA, Diverticular Inflammation and Complication Assessment; CODA, Combined Overview on Diverticular Assessment; FC, fecal calprotectin.

of constipation (i.e., $VAS_{constipation}=0$) and 10.0% (95% CI, 7.0%–13.7%) in patients with these specific symptoms ($VAS_{constipation}>0$), which significantly differed across the strata (log-rank test, $P=0.03$) (Fig. 2A). Similarly, the estimated 3-year cumulative probability of diverticulitis was 6.2% (95% CI, 4.4%–8.6%) in patients with no symptoms of diarrhea ($VAS_{diarrhea}=0$) and 9.7% (95% CI, 6.6%–13.5%) in patients with $VAS_{diarrhea}>0$. However, this latter difference was slightly above the statistical significance threshold (log-rank test, $P=0.06$) (Fig. 2B).

DISCUSSION

Although the worldwide DD prevalence is well known, and its main complication, acute diverticulitis, is now easy to recog-

Table 2. Effect of Constipation and Diarrhea on the Risk of Acute Diverticulitis: Time-to-Event Analysis

Baseline parameter	Multivariable Cox PH model	
	HR (95% CI)	*P*-value
Constipation (per 1-VAS point increase)	1.15 (1.04–1.27)	0.004
Diarrhea (per 1-VAS point increase)	1.14 (1.03–1.26)	0.014
Sex (males vs. females)	1.51 (0.92–2.49)	0.104
Age (per 1-yr increase)	0.97 (0.95–0.99)	0.016

PH, proportional-hazard; HR, hazard ratio; CI, confidence interval; VAS, visual analog scale.

nize, it is still unclear whether bowel habits frequency may be linked to the severity of the disease and/or with the risk of acute diverticulitis. In particular, whether constipation or diarrhea is related to the risk of developing acute diverticulitis.

For many years, DD has been thought to be strictly linked to constipation. In particular, the demonstration that defecation in a sitting position, with a reduction of the anorectal angle and increase of intra-colonic pressure,[15] has been considered one of the causes of the increasing prevalence of DD in the Western World. However, several studies from the United

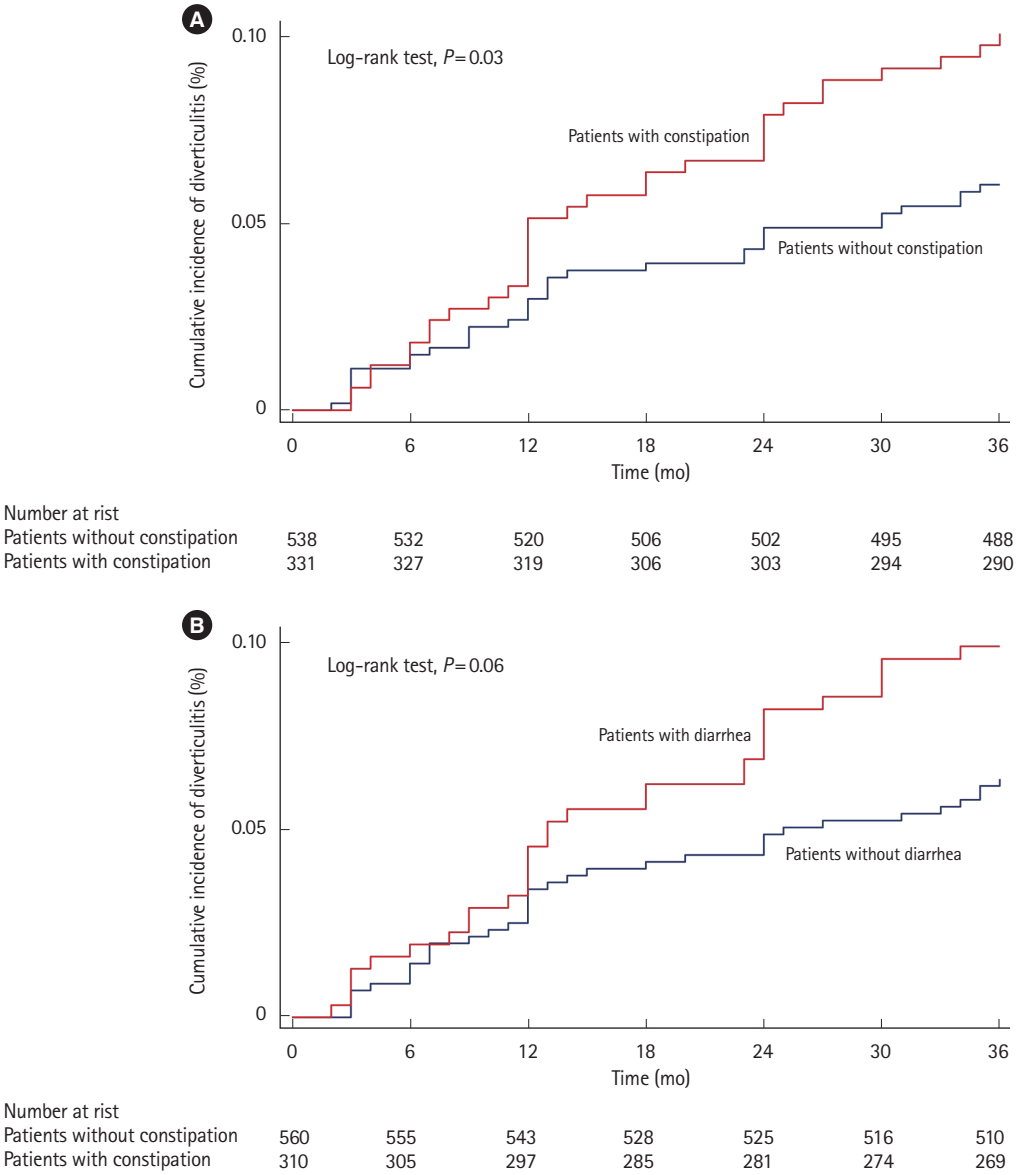

Fig. 2. Kaplan-Meier curves of the cumulative incidence of acute diverticulitis. (A) Comparison between patients without symptoms of constipation (10-point VAS = 0) and patients reporting any symptom of constipation (10-point VAS ≥ 1). (B) Comparison between patients without symptoms of diarrhea (10-point VAS = 0) and patients reporting any diarrhea (10-point VAS ≥ 1). Two-sided *P*-values from log-rank tests are reported. VAS, visual analog scale.

States[6-8,16] and Japan[9,17] failed to find an association between constipation and diverticulosis. On the contrary, diarrhea and loose stools were associated with DD in the United States[16] and Japan.[14] And looking at the risk of acute diverticulitis according to bowel habits frequency, it has been recently shown that diarrhea, not constipation, may be a risk factor for acute diverticulitis, especially in women.[10] However, these symptoms have only sometimes been compared with the severity of the disease nor with FC expression.

This is the first study in which the frequency of bowel habits was compared with the severity of DD using objective methods. We found that higher scores of constipation and diarrhea at baseline correlated with higher endoscopic (i.e., DICA) and composite (CODA) scores of DD severity. This means that patients undergoing colonoscopy and complaining of abnormal bowel habits are at higher risk of having a more severe disease, whether diverticulosis is detected. Why this occurs is unknown. Colonic motility, which in these patients often displays abnormal motor patterns frequently associated with pain,[18] is likely to play an important role, as also shown by the abnormalities of the enteric nervous system reported in patients with DD.[19] Also, bowel habit abnormalities may be linked to intraluminal factors. There is evidence that stool consistency[20,21] and bowel movement frequency[22,23] may modify the intestinal microbiome, even though it is not known whether altered gut motility influences[22,23] the changes in the gut microbiome or is influenced by the changes in the gut microbiome.[24,25] However, the recent observations about the changes in colonic microbiome in acute diverticulitis, even according to the severity of the disease,[26] may shed light on potential mechanisms that underlie the association between severity of bowel movement frequency, severity of DD and risk of acute diverticulitis.

Intestinal inflammation may also be essential in determining the risk of acute diverticulitis in those patients, as shown by the presence of low-grade inflammation in mucosa biopsy[27] and resected surgical specimens.[28] We recently reported that FC of 90 μg/g is the cutoff for the risk of acute diverticulitis.[11] In the present study, we found that higher scores of constipation and diarrhea were associated with higher basal FC, thus suggesting that higher scores of constipation and diarrhea are associated with higher inflammation, which might lead to acute diverticulitis. The detection of myenteric plexitis (namely, the infiltration of myenteric ganglions by inflammatory cells) in patients undergoing surgery for DD seems to confirm this hypothesis.[28]

Whatever the underlying mechanisms, we found that constipation and diarrhea are independent risk factors for acute diverticulitis. This is an important point because, after adjusting for sex and age (factors potentially influencing the risk of acute diverticulitis occurrence),[9,10] each of these bowel habits may independently affect the outcome of the disease. This result is strengthened by the multivariate analysis showing that, after adjusting for age and sex, each point of constipation score increased the risk of acute diverticulitis by approximately 15%, and each point of diarrhea score increased this risk by about 14%. This means that not only the severity of constipation or diarrhea in patients with DD is associated with the severity of the disease, but also that the increase in the score of constipation or diarrhea increases the hazard of acute diverticulitis. This means that not only the severity of constipation or diarrhea is associated with the severity of DD, but also that the higher constipation or diarrhea score, the higher hazard of acute diverticulitis. Putting all together these data, we can draw essential recommendations for the clinical practice: patients having diverticulosis and complaining of more severe constipation or diarrhea may have worse endoscopic and inflammation scores and are at increased risk of developing diverticulitis, thus needing closer monitoring.

We are aware that this study has some limitations. For instance, we do not have information about diet; a high-fiber diet is still recommended to prevent DD complications.[29] Thus, we cannot exclude that constipation or diarrhea may be due to a lower or higher volume of fiber intake. Another area for improvement is the need for more information on ongoing treatments for bowel habit alterations. Unfortunately, these data were unavailable during patients' enrollment, and this *post-hoc* analysis does not permit overcoming this limitation. Lastly, the study was conducted on a subset of patients with valid FC measurements. We recognize this may introduce a selection of participants and, therefore, partially limit the generalizability of the findings.

In conclusion, this prospective cohort study showed that higher diarrhea and constipation scores at baseline predicted higher endoscopic (i.e., DICA) and composite (i.e., CODA) scores of DD severity and higher FC levels. Moreover, both constipation and diarrhea were independent prognostic factors of acute diverticulitis. Additional studies are needed to elucidate this association's potential mechanisms, providing new targets for managing DD and preventing acute diverticulitis.

ADDITIONAL INFORMATION

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Conflict of Interest

Tursi A served as speaker and/or consultant for AbbVie, Galápagos, Janssen, Nalkein, and Omega Pharma. Maconi G served as speaker and/or advisory board fees for AlfaSigma, Arena, Janssen, Gilead, and Roche. Nardone G received funding for target projects from Apharm and Sofar. Pietrzak A served as a lecturer for AlfaSigma and Polpharma. Regula J served as a lecturer for AlfaSigma, Takeda, Ipsen, and Servier. Scaldaferri F served as a lecturer for AbbVie, Celltrion, Ferring, Janssen, Lilly, Pfizer, Sanofi, and Takeda. Papa A served as a speaker for Janssen. Danese S served as speaker, consultant, and/or advisory board member for AbbVie, Allergan, Alfa Wassermann, Biogen, Boehringer Ingelheim, Celgene, Celltrion, Ferring, Gilead, Hospira, Johnson & Johnson, Merck, MSD, Mundipharma, Pfizer Inc., Sandoz, Takeda, Tigenix, UCB Pharma, Vifor. The remaining authors declare no competing interests.

Data Availability Statement

All data and related metadata underlying the findings reported in the manuscript are deposited in an appropriate public repository, unless already provided as part of the article.

Author Contributions

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Supplementary Material

Supplementary materials are available at the Intestinal Research website (https://www.irjournal.org).

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